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STRATEGIES FOR DISCONTINUING PSYCHOTROPIC MEDICATIONS

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Abstract

Psychotropic medications include antidepressants, antipsychotics, stimulants, mood stabilizers, anxiolytics, sedative–hypnotics, and, arguably, cognitive enhancers. These agents cross the blood–brain barrier and can alter perception, mood, consciousness, cognition, and behaviour. Psychotropic medications are extensively used and pose challenges when they are stopped. Re-emergence of the patient's initial symptoms as well as withdrawal syndromes can occur, especially if these medications are stopped abruptly. As a general rule, dosages should be slowly decreased when discontinuing the medications. It is recommended that patients be carefully monitored for withdrawal symptoms and recurrence of their psychiatric symptoms as the psychotropics are being tapered and immediately after stopping them. This article presents an overview of the scope, type of withdrawal symptoms that might be encountered, and approaches to stopping sedative–hypnotics, antidepressants, antipsychotics, and cholinesterase inhibitors. When done in a careful manner, discontinuation of these drugs can be successfully implemented in many patients.

Résumé

Les médicaments psychotropes englobent les antidépresseurs, les antipsychotiques, les psychostimulants, les stabilisateurs de l'humeur, les anxiolytiques, les sédatifs-hypnotiques et probablement (bien que sujet à une certaine controverse) les potentialisateurs cognitifs utilisés en démence. Les médicaments psychotropes sont d'usage répandu et l'arrêt de ceux-ci n'est pas nécessairement aisé. Il peut y avoir soit une récurrence des symptômes initiaux du patient, soit des syndromes de sevrage- et ce plus particulièrement lorsque les traitements sont cessés abruptement. En règle générale, la posologie de ces médicaments doit être diminuée de façon progressive avant de procéder à l'arrêt complet de ceux-ci. Il est recommandé de suivre les patients étroitement pendant la diminution de la posologie et suite à l'arrêt complet du médicament, en demeurant à l'affût des symptômes de sevrage et de la récurrence des symptômes psychiatriques. Dans cet article, on présente une revue générale de la problématique associée à l'utilisation des médicaments psychotropes, les types de symptômes de sevrage possibles ainsi que l'approche qui devrait être utilisée pour sevrer ces médicaments. Lorsque le sevrage est fait de façon appropriée, l'arrêt des médicaments psychotropes est possible chez un grand nombre de patients.

Case Presentation

Mrs. SG is an 86-year-old resident of an assisted living facility. You took on her care when she was admitted a month ago. For her intake case conference, you reviewed her medications and noted that she had been on risperidone twice daily, citalopram once daily, and lorazepam at bedtime for approximately 2 years. These medications were started when her husband passed away. Facility staff has no concerns about her behaviour. She denies any significant depressive, psychotic, or sleep-related symptoms. Over the last year, she has been on donepezil for Alzheimer disease at a moderate stage. At the case conference, her family asks if any of the medications should be discontinued.

Introduction

Psychotropic (or psychoactive) medications cross the blood–brain barrier and can alter perception, mood, consciousness, cognition, and behavior. These agents include antidepressants, antipsychotics, stimulants, mood stabilizers, anxiolytics, and sedative–hypnotics. Some hold that cholinesterase inhibitors have psychotropic as well as cognition-enhancing effects.

Sedative-–Hypnotics

Benzodiazepines are often used to treat insomnia. Trials have shown moderate short-term efficacy. They are also prescribed for other conditions such as anxiety disorders and seizures. Problems with their use

Table 1. Summary of Adverse Effects and Withdrawal Syndromes of Select Psychotropic Medications

Class	Examples	Adverse Effects/ Warnings	Withdrawal Syndrome
Antidepressants			
Selective Serotonin Reuptake Inhibitors[11]	Citalopram, escitalopram, fluoxetine, fluvoaxamine, paroxetine, and sertraline	Anticholinergic effects (especially paroxetine),[14] orthostatic hypotension, tachycardia, agitation, akathisia, fatigue, headache, insomnia, nausea, yawning, sweating, weight gain, diarrhea, dyspepsia, nausea, arthralgia, myalgia, upper respiratory tract infections Select warnings: serotonin syndrome if taken with MAO inhibitor; older patients may be more susceptible to dose-related QT prolongation(especially with citalopram & escitalopram), hyponatremia and bleeding	Can occur following abrupt discontinuation or dosage reduction; symptoms include dizziness, nausea, fatigue, headache, and/or insomnia
Cyclic Antidepressants[12, 13]	Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, and trimipramine	Orthostatic hypotension, ventricular arrhythmias, heart block, sexual dysfunction, weight gain, anticholinergic effects, sedation Select warnings: anti-cholinergic effects and orthostatic hypotension may be more common in older patients; lower starting dose and more gradual dose titration recommended, with desipramine and nortriptyline being favoured agents	Abrupt withdrawal can lead to symptoms such as akathisia, anxiety, headache, dizziness, nausea, and/or vomiting
Antipsychotics[17,18]			
	Haloperidol (first-generation agent); risperidone, olanzapine, and quetiapine (second-generation agents)	Extrapyramidal symptoms (dystonia, parkinsonism akathisia, tardive dyskinesia; more common in first-generation agents), orthostatic hypotension, QT prolongation, tachycardia, weight gain, dyslipidemia, diabetes, hyperprolactinemia, anticholinergic effects *Select warning:* Increased mortality in older patients with dementia treated with antipsychotics	Abrupt withdrawal can lead to nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and/or insomnia within 48 hours of the last dose; withdrawal/emergent and covert dyskinesia can occur[24]
Sedative-Hypnotics			
Benzodiazepines[3]	Alprazolam, bromazepam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, and temazepam	Dose-dependent ataxia, dizziness, light-headedness, drowsiness, weakness, fatigue; dependency/ tolerance risk with prolonged use *Select warnings:* Older patients more likely to experience central nervous system (CNS) adverse effects; long-acting agents such as diazepam and flurazepam should be avoided in older patients	Abrupt withdrawal can lead to anxiety, insomnia, psychomotor agitation, gastrointestinal (GI) discomfort, tremor, anorexia, diaphoresis, tachycardia, photophobia/phonophobia and/ or rebound insomnia; severe withdrawal symptoms can include delirium and seizures

include the potential for side effects (e.g., daytime somnolence and fatigue, cognitive impairment, and increased risk of falls and fractures), development of dependence and tolerance, and withdrawal symptoms (i.e., anxiety, insomnia, nightmares, stiffness, weakness, gastrointestinal disturbances, and flulike symptoms) when discontinued after 4 to 6 weeks or more of continuous use (Table 1).[2,3] Even if initially prescribed to deal with a time-limited issue, these medications often are taken for lengthy periods despite the lack of long-term safety and efficacy data. Approximately a third of patients who have used these agents over the long term will encounter withdrawal symptoms. Shorter-acting benzodiazepines (e.g., lorazepam) are more likely to lead to withdrawal symptoms compared with agents with a longer duration of action (e.g., diazepam). To avoid this problem, continuous therapy should be limited to no more than 4 weeks. Intermittent use (i.e., not daily) might also be helpful. Notwithstanding the challenges, it would be reasonable to try to discontinue lorazepam in the resident described, although it would be important to gauge her willingness to do this. Abrupt stopping of these drugs after long-term use should be avoided because of the risk of withdrawal symptoms, which can be severe (e.g., delirium and seizures).

Approaches to Stopping

Even minimal interventions (e.g., a letter or an in-person consultation where the practitioner expresses concern over the long-term use of these drugs, outlines potential side effects, and provides advice for gradually reducing them to minimize the likelihood of withdrawal symptoms) can have a significant impact on long-term benzodiazepine use.[2,4] More intensive approaches, however, such as supervised tapering (i.e., while under care, gradually reducing the dosage of a particular drug used by a patient) over an 8- to 10+-week period possibly combined with cognitive–behavioural therapy are often needed to achieve discontinuation among chronic users.[5–8]

Before tapering benzodiazepines that have a short or intermediate half-life, some advocate switching to an equivalent dose of diazepam because its long half-life would be associated with less severe withdrawal symptoms. There is little research to support this approach,[6] and there are concerns about the prolonged sedating effect seen with the long-acting benzodiazepines. The author of this article, however, does not make this switch. Although gradual and progressive reduction over 8 to 10+ weeks is recommended, there are no precise rules to guide practice. A flexible approach based on certain principles is recommended. The drug should be given on a scheduled basis rather than as required. Generally, you reduce more gradually as you get to lower dosages (i.e., taper by 10% of the dose every 1 to 2 weeks until you reach 20% of the original dose and then taper by 5% every 2 to 4 weeks). Halt or reverse the tapering if severe withdrawal symptoms occur. The patients must be monitored regularly (every 1 to 4 weeks) during the withdrawal phase. The patient should be supported during this process and the benefits of coming off the agent reinforced at meetings. Adjunctive therapies such as antidepressants, mood stabilizers (e.g., carbamazepine), and melatonin may be considered but are not recommended for routine use.[2,6]

Antidepressants

The therapeutic effects of antidepressants do not persist once they are stopped. To minimize the risk of relapse the 2010 American Psychiatric Association practice guidelines recommended carrying on with antidepressants for 4 to 9 months following resolution of the symptoms of a major depressive disorder http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-guide.pdf. Other guidelines suggest even longer periods of initial therapy.[9,10] Although a thorough psychiatric history is clearly needed for the patient in the case discussed here, the patient reported no depressive symptoms and had been on citalopram for 2 years. In addition to being no longer indicated, continued use exposes the patient to the risk of experiencing one of the numerous adverse effects associated with these drugs (see Table 1).[11,12,14] Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, which the resident is taking, can cause nausea, dry mouth, somnolence, insomnia, increased perspiration, tremor, diarrhea, sexual dysfunction, serotonin syndrome (from excess serotonergic activity leading to restlessness, diaphoresis, tremors, shivering, myoclonus, and, when severe, confusion, seizures, and even death), and other side effects such as hyponatremia (from a syndrome of inappropriate antidiuretic hormone secretion), inhibition of serotonin-mediated platelet activation with an increased risk of gastrointestinal bleeding (and possibly hemorrhagic stroke), osteoporosis[14], and prolongation of the Q–T interval.

Discontinuation symptoms can occur with all antidepressant classes. An important determinant of the appearance and severity of these symptoms is the pharmacokinetics of the agent (e.g., antidepressants such as venlafaxine and paroxetine, which have shorter half-lives are more likely to be associated with withdrawal symptoms). An acronym for the more common symptoms encountered is FINISH for Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (i.e., anxiety/ agitation).[15] Withdrawal symptoms can affect up to a third of treated patients and usually develop within 5 days of stopping the agent. In most patients, the symptoms are self-limiting and mild, although they can be severe in some individuals.

Approaches to Stopping

If an antidepressant has been administered continuously for 6 to 8+ weeks, rather than stopping the drug abruptly, whenever possible, the dose should be gradually reduced until the drug is discontinued. Of course, abruptly stopping an antidepressant is justified if a patient has developed serious adverse effects from the agent (e.g., cardiac arrhythmia from a cyclic

antidepressant) or there is a medical emergency requiring its discontinuation. Tapering is typically done over a 4+-week period. Toward the end of the taper, dose reductions should be done more gradually.[2,16] The specific regimen used is more a matter of opinion than science, as no particular approach is supported by rigorous research data. Some patients may prefer to stop abruptly in order to get off the drug and through the withdrawal phase more quickly. A reasonable rule of thumb is to base the pace of the taper (and its duration) on the response of the patient to prior dosage reductions. Generally, antidepressants with shorter half-lives (e.g., venlafaxine, paroxetine) are tapered more slowly (e.g., reducing dosage by 25% every 4 to 6 weeks). In the absence of any intention to switch to another antidepressant, there is no time pressure on the duration of the taper. If switching to another antidepressant, the second or new agent could be slowly introduced as the ineffective or poorly tolerated one is withdrawn. This is called *cross-tapering*.[2] Whether this should be considered and how quickly it could be done depend on the nature of the switch being contemplated (e.g., if switching from one SSRI to another, it would be simpler to discontinue the first agent abruptly and start the second SSRI right away, as it would likely ameliorate any symptoms that might be caused by the discontinuation), on the recommended titration schedule for the new agent, and on the response of the patient. Few studies are available to guide practice, so the cross-tapering should be done cautiously. In case of unfamiliarity with the process, it would be wisest not to use this approach. Potential hazards of cross-tapering would include augmented drug effects (e.g., development of a serotonin syndrome). Remember that the coadministration of certain antidepressants (SSRIs and monoamine oxidase [MAO] inhibitors) is contraindicated.

Antipsychotics

Antipsychotics are frequently used to treat some of the neuropsychiatric symptoms (NPSs) that can arise in the setting of dementia. Nonpharmacological approaches to the prevention and management of NPSs should be considered first, but if ineffective short term (e.g., 3–6 months) use of antipsychotics may help in dealing with specific NPSs where there is a risk of harm to the patient, others, or both. These drugs are modestly effective for psychotic symptoms (delusions and hallucinations), aggression, or severe agitation.[17] Their use is associated with a number of side effects such as sedation, falls and injuries, parkinsonism, akathisia, tardive dyskinesia, accelerated cognitive decline, sexual dysfunction, weight gain, development of diabetes, and a higher risk of stroke and death when used in persons with dementia (see Table 1).[18,19] Treating an older patient suffering from dementia with a second-generation (or atypical) antipsychotic for 10 to 12 weeks is associated with an approximately 1.5-fold higher risk of death, which translates to an absolute increase of about 1% in the risk of dying.[20] The potential benefits of these drugs must be weighed against their significant risk of harm. An audit from the United Kingdom reported that the use of antipsychotics was potentially inappropriate in up to two-thirds of those with dementia taking these drugs.[21] A Cochrane systematic review concluded that many patients with Alzheimer disease and NPSs treated with antipsychotics could have them stopped without detrimental effects on behaviour.[22] Attempts to discontinue these agents should be incorporated into routine practice with two qualifications: (1) after stopping, patients should be carefully monitored, as there may be an increased risk of relapse among those whose agitation or psychosis had initially responded well to antipsychotic treatment;[23] and, (2) patients with more severe NPSs might benefit from the continued use of an antipsychotic.[22] As the resident described in the case had no indication for the use of an antipsychotic, cessation of this medication should be considered.

Approaches to Stopping

Antipsychotics should be gradually tapered to minimize the likelihood of occurrence of discontinuation symptoms. Subsequent to coming off an antipsychotic, the patient should be monitored for recurrence of NPSs.[22,23] Withdrawal emergent or covert dyskinesias can develop after stoppage of an antipsychotic.[24] Both resemble tardive dyskinesia, but the former is self-limiting (generally disappearing within 12 weeks), whereas covert dyskinesia does not go into remission spontaneously (i.e., the antipsychotic was suppressing the movements that become evident after the drug is stopped). A variety of treatment approaches can be considered if the dyskinesias persist.[25]

Cholinesterase Inhibitors

Mrs. G is on a cholinesterase inhibitor (donepezil). Once a person is on the medication, it does not mean that he or she should remain on it indefinitely. Discontinuing a cholinesterase inhibitor might lead to worsening of the person's cognitive and functional status, but this must be balanced with the risk of side effects and costs of therapy.[17] Criteria for stopping would include the patient (or proxy decision maker) deciding to stop the drug, significant nonadherence that cannot be corrected, cognitive and functional decline occurring more rapidly than before treatment was started, intolerable side effects (e.g., anorexia, weight loss,

Key Points

- *Withdrawal of a psychotropic should be done gradually, whenever possible.*
- *Patients should be carefully monitored for withdrawal symptoms and recurrence of psychiatric symptoms while the psychotropic is being tapered and immediately thereafter.*
- *Toward the end of a taper, dose reductions should be done more gradually.*

nausea, vomiting, diarrhea, leg cramps, insomnia, hyperstimulation with irritability or agitation, excessive sweating, increased urinary incontinence, rhinorrhea, etc.), presence of comorbidities making treatment with a cholinesterase inhibitor either too risky (e.g., syncope) or futile (e.g., terminal illness), or progression to a stage where no clinically meaningful benefit would be expected.[17]

Approaches to Stopping

When a cholinesterase inhibitor is stopped because of perceived lack of effectiveness, the agent should be tapered, if possible. After the agent is discontinued, the patient should be monitored over the next 1 to 3 months for evidence of cognitive deterioration, functional deterioration, or both (with consideration of restarting if this occurs).[17]

Conclusions

After consulting with the resident and her family, it was agreed that she would be left on donepezil but that an attempt would be made to stop her risperidone, citalopram, and lorazepam. This was done in a staged manner, with the risperidone dealt with first followed by citalopram (each over 4 weeks) and then lorazepam (over 14 weeks). All three drugs were successfully discontinued.

Conflict of Interest

None to declare.

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